RATE CONTROLLING MEMBRANES FOR CONTROLLED DRUG DELIVERY DEVICES

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 60/068,377, filed on December 22, 1997.

FIELD OF THE INVENTION

[0002] This invention relates to the field of drug delivery devices which incorporate a rate controlling membrane in order to control the rate of release of a drug from the device to a patient. More particularly, the invention is directed to rate controlling membranes for drug delivery devices characterized by being subjected to an annealing process in accordance with the present invention. The rate controlling membranes of this invention exhibit improved membrane functionality particularly with respect to storage time.

BACKGROUND OF THE INVENTION

[0003] The use of rate controlling membranes to control delivery of a drug from a drug delivery device is well known. For example, transdermal drug delivery devices including rate controlling membranes are disclosed in U.S. Patent Nos. 3,797,494, 4,031,894, 4,201,211, 4,379,454, 4,436,741, 4,588,580, 4,615,699, 4,661,105, 4,681,584, 4,698,062, 4,725,272, 4,832,953, 4,908,027, 5,004,610, 5,310,559, 5,342,623, 5,344,656, and 5,364,630, which are incorporated in their entirety herein by reference. As disclosed in these patents, various materials, including ethylene vinyl acetate

copolymers and polyethylene, may be used to form rate controlling membranes useful for transdermal drug delivery systems. Additional materials useful for forming rate controlling membranes for transdermal drug delivery devices are disclosed in K.P.R. Chowdary et al. "*Preparation and Evaluation of Cellulose Acetate Films as Rate Controlling Membranes for Transdermal Use*" Indian Drugs 29 (7).

[0004] For a selected membrane material, after conversion of the polymer pellet to the membrane, the necessary rate control for a transdermal drug delivery device is provided by varying the composition, pore size, or thickness of the rate controlling membrane, adjusting the viscosity of the drug formulation to be administered by appropriate formulation, or impregnating the pores of the membranes with a diffusive medium as disclosed in US Patent No. 3,797,494 listed above. The rate controlling membrane is then incorporated into a transdermal drug delivery device without any other additional treatment thereof.

[0005] Diffusional and osmotically driven fluid-imbibing dosage forms incorporating rate controlling membranes are also known in the art. For example, U.S. Patent Nos. 3,845,770 and 3,916,899, incorporated herein by reference, disclose a device comprising a wall that surrounds a compartment containing a drug for delivery to a patient. The wall of the device is permeable to the passage of fluid. Drug is released from the device by fluid being imbibed through the wall into the device at a rate determined by the permeability of the wall and the osmotic pressure gradient across the wall. Other diffusional and osmotic fluid-imbibing dosage forms are disclosed in U.S. Patent Nos. 3,987,790, 4,111,202, 4,111,203, 4,203,439, 4,327,725, 4,612,008, 4,865,845, 5,034,229, 5,057,318, 5,059,423, 5,110,596, 5,112,614, 5,137,727, 5,234,692, and 5,234,693, all of which are hereby incorporated in their entirety by reference.

[0006] Additionally, US Patent Nos. 4,931,295, 5,024,842, and 5,160,743 disclose a dosage form comprising a coat surrounding a drug. The

coat comprises a water soluble overcoat polymer and a subcoat. The overcoat and the subcoat are annealed to provide a continuous, insoluble membrane or film that surrounds the drug and which dissolves in an aqueous environment of use.

[0007] One problem associated with prior art rate controlling membranes formed from thermoplastic polymers is that they often encounter morphological changes after processing over long periods of time due to phase separation of domain structures. These morphological changes can alter the membrane functionality. For example, the water permeation or water uptake rate through the membrane of fluid-imbibing devices may vary over time, leading to inconsistent performance of the device.

[0008] Another problem associated with prior art rate non-annealed rate controlling membranes used in controlled drug delivery devices is that the permeability of the membrane may vary over the storage period, particularly when such devices are exposed to elevated temperatures. If this occurs, the system would not have a drug release rate which is stable as a function of storage time. This is particularly undesirable where, for example, the permeability of the rate controlling membrane to the drug is increased beyond a preferred range due to exposure of the system to elevated temperatures.

[0009] Variations in the rate of administration of drugs can effect efficacy and cause undesirable side effects. As can be appreciated by one of ordinary skill in the art, variations in the functionality of rate controlling membranes of drug delivery devices over storage may arise in any device which incorporates a rate controlling membrane and can pose a significant problem.

<u>BRIEF DESCRIPTION OF TERMS</u>